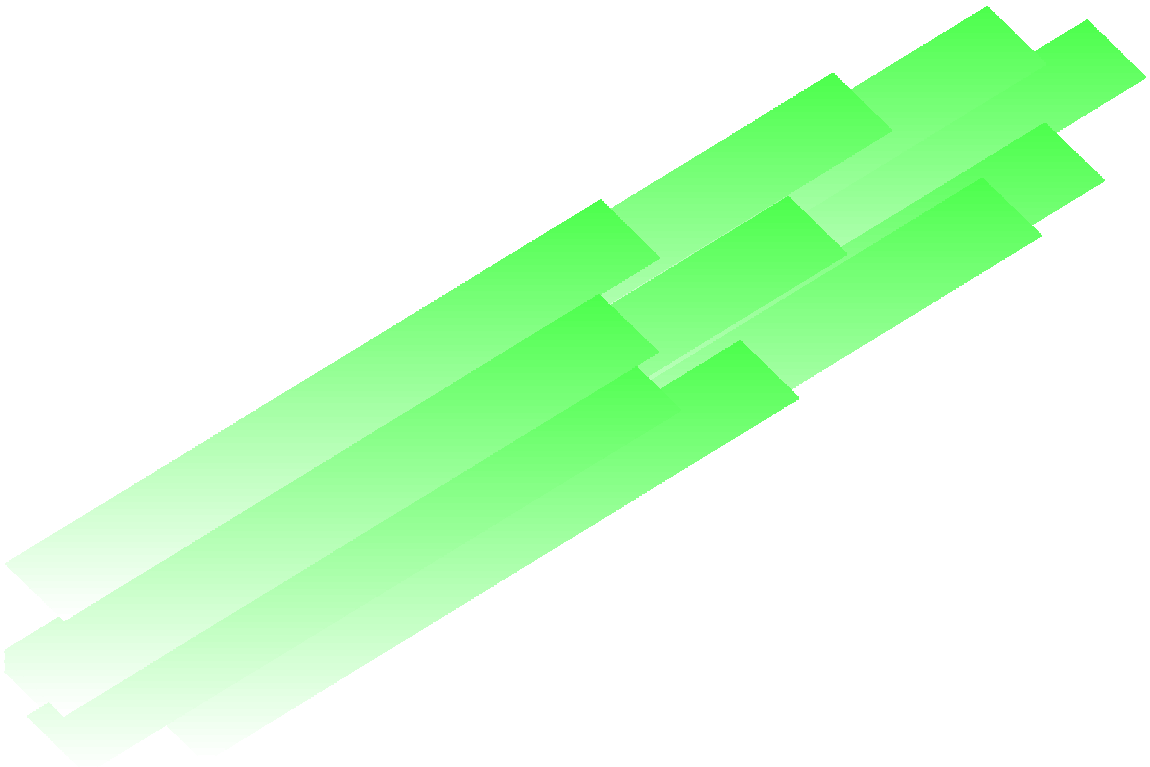
Guidance for Industry

Labeling Guidance for Clindamycin Phosphate Injection, USP



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1998
OGD-L-38-R-1

Guidance for Industry

Labeling Guidance for Clindamycin Phosphate Injection, USP

Additional copies are available from:

Office of Generic Drugs
Division of Labeling and Program Support
Labeling Review Branch II
Attention: Team Leader
MetroPark North II
7500 Standish Place, Room 266N
Rockville, MD 20855-2773

(Tel) 301-827-5846
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1998
OGD-L-38-R-1

GUIDANCE FOR INDUSTRY[1]

Labeling Guidance for Clindamycin Phosphate Injection, USP

I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (Cleocin Phosphate® Sterile Solution; Pharmacia & Upjohn; 50-639/S-011 and S-012; Approved June 8, 1998; Revised December 1997). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

See next page.

[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

CLINDAMYCIN PHOSPHATE INJECTION USP

℞ only

WARNING

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS AND USAGE section. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

DESCRIPTION

Clindamycin phosphate injection, a water soluble ester of clindamycin and phosphoric acid, is a sterile solution for intramuscular or intravenous use.

Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

The chemical name of clindamycin phosphate is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate).

The molecular formula is $C_{18}H_{34}ClN_2O_8PS$ and the molecular weight is 504.97.

The structural formula is represented below:

[Note: Insert structural formula here.]

Each mL contains clindamycin phosphate equivalent to 150 mg clindamycin, 0.5 mg disodium edetate and 9.45 mg benzyl alcohol added as a preservative.

CLINICAL PHARMACOLOGY

Biologically inactive clindamycin phosphate is rapidly converted to active clindamycin.

By the end of short-term intravenous infusion, peak serum levels of active clindamycin are reached. Biologically inactive clindamycin phosphate disappears rapidly from the serum; the average elimination half-life is 6 minutes; however, the serum elimination half-life of active clindamycin is about 3 hours in adults and 2½ hours in children.

After intramuscular injection of clindamycin phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in pediatric patients. Serum level curves may be constructed from IV peak serum levels as given in Table 1 by application of elimination half-lives listed above.

Serum levels of clindamycin can be maintained above the *in vitro* minimum inhibitory concentrations for most indicated organisms by administration of clindamycin phosphate every 8 to 12 hours in adults and every 6 to 8 hours in children, or by continuous intravenous infusion. An equilibrium state is reached by the third dose.

The elimination half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease.

No significant levels of clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges.

Pharmacokinetic studies in elderly volunteers (61 to 79 years) and younger adults (18 to 39 years) indicate that age alone does not alter clindamycin pharmacokinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentration-time curve) after IV administration of clindamycin phosphate. After oral administration of clindamycin hydrochloride, elimination half-life is increased to approximately 4 hours (range 3.4 to 5.1 h) in the elderly compared to 3.2 hours (range 2.1 to 4.2 h) in younger adults. The extent of absorption, however, is not different between the age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function[1].

Serum assays for active clindamycin require an inhibitor to prevent *in vitro* hydrolysis of clindamycin phosphate.

Table 1. Average Peak and Trough Serum Concentrations of Active Clindamycin After Dosing with Clindamycin Phosphate

Dosage Regimen	Peak mcg/mL	Trough mcg/mL
Healthy Adult Males (Post equilibrium)		
600 mg IV in 30 min q6h	10.9	2.0
600 mg IV in 30 min q8h	10.8	1.1
900 mg IV in 30 min q8h	14.1	1.7
600 mg IM q12*	9	
Children (first dose)*		
5-7 mg/kg IV in 1 hour	10	
5-7 mg/kg IM	8	
3-5 mg/kg IM	4	

*Data in this group from patients being treated for infection.

Microbiology: Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms:

Aerobic gram positive cocci, including:
- *Staphylococcus aureus* (penicillinase and non-penicillinase producing strains).
- *Staphylococcus epidermidis* When tested by *in vitro* methods, some staphylococcal strains originally resistant to erythromycin rapidly develop resistance to clindamycin.
- Streptococci (except *Enterococcus faecalis*)
- Pneumococci

Anaerobic gram negative bacilli, including:
- *Bacteroides* species (including *Bacteroides fragilis* group and *Bacteroides melaninogenicus* group)
- *Fusobacterium* species

Anaerobic gram positive nonsporeforming bacilli, including:
- *Propionibacterium*
- *Eubacterium*
- *Actinomyces* species

Anaerobic and microaerophilic gram positive cocci, including:
- *Peptococcus* species
- *Peptostreptococcus* species

Microaerophilic streptococci

Clostridia: Clostridia are more resistant than most anaerobes to clindamycin. Most *Clostridium perfringens* are susceptible, but other species, e.g., *Clostridium sporogenes* and *Clostridium tertium* are frequently resistant to clindamycin. Susceptibility testing should be done.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

***In vitro* Susceptibility Testing**:

Disk diffusion technique--Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure[2] has been recommended for use with disks to test susceptibility to clindamycin.

Reports from a laboratory using the standardized single-disk susceptibility test[1] with a 2 mcg clindamycin disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 17 mm or greater, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones of 15-16 mm, indicating that the tested organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Standardized procedures require the use of control organisms. The 2 mcg clindamycin disk should give a zone diameter between 24 and 30 mm for *S. aureus* ATCC 25923.

Dilution techniques - A bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) for clindamycin is not more than 1.6 mcg/mL. Organisms are considered moderately susceptible if the MIC is greater than 1.6 mcg/mL and less than or equal to 4.8 mcg/mL. Organisms are considered resistant if the MIC is greater than 4.8 mcg per mL.

The range of MIC's for the control strains are as follows:

S. aureus ATCC 29213, 0.06 to 0.25 mcg/mL.
E. faecalis ATCC 29212, 4.0 to 16 mcg/mL.

For anaerobic bacteria the minimum inhibitory concentration (MIC) of clindamycin can be determined by agar dilution and broth dilution (including microdilution) techniques.[3] If MICs are not determined routinely, the disk broth method is recommended for routine use. THE KIRBY-BAUER DISK DIFFUSION METHOD AND ITS INTERPRETIVE STANDARDS

ARE NOT RECOMMENDED FOR ANAEROBES.

INDICATIONS AND USAGE

Clindamycin phosphate injection is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin phosphate injection is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of antibiotic-associated pseudomembranous colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Clindamycin phosphate injection is indicated in the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, *Streptococcus pneumoniae*, other streptococci (except *E. faecalis*), and *Staphylococcus aureus*.

Skin and skin structure infections caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, and anaerobes.

Gynecological infections including endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection caused by susceptible anaerobes.

Intra-abdominal infections including peritonitis and intra-abdominal abscess caused by susceptible anaerobic organisms.

Septicemia caused by *Staphylococcus aureus*, streptococci (except *Enterococcus faecalis*), and susceptible anaerobes.

Bone and joint infections including acute hematogenous osteomyelitis caused by *Staphylococcus aureus* and as adjunctive therapy in the surgical treatment of chronic bone and joint infections due to susceptible organisms.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

WARNINGS

See **WARNING** box.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants. (See PRECAUTIONS--Pediatric Use).

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General

Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Clindamycin phosphate should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Clindamycin phosphate should be prescribed with caution in atopic individuals.

Certain infections may require incision and drainage or other indicated surgical procedures in addition to antibiotic therapy.

The use of clindamycin phosphate may result in overgrowth of nonsusceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Clindamycin phosphate should not be administered intravenously undiluted as a bolus, but should be infused over at least 10 to 60 minutes as directed in the DOSAGE AND ADMINISTRATION section.

Clindamycin dosage modification may not be necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of clindamycin half-life has been found. However, it was postulated from studies that when given every eight hours, accumulation should rarely occur. Therefore, dosage modification in patients with liver disease may not be necessary. However, periodic liver enzyme determinations should be made when treating patients with severe liver disease.

Laboratory Tests
During prolonged therapy periodic liver and kidney function tests and blood counts should be performed.

Drug Interactions
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic effects
Pregnancy Category B
Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (2.1 and 1.1 times the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (0.9 and 0.5 times the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if it is clearly needed.

Nursing Mothers
Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for adverse reactions due to clindamycin in neonates (see **Pediatric Use**), the decision to discontinue the drug should be made, taking into account the importance of the drug to the mother.

Pediatric Use
When clindamycin phosphate injection is administered to the pediatric population (birth to 16 years) appropriate monitoring of organ system functions is desirable.

Usage in Newborns and Infants
This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants.

Geriatric Use
Clinical studies of clindamycin did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients. However, other reported clinical experience indicates that antibiotic-associated colitis and diarrhea (due to *Clostridium difficile*) seen in association with most antibiotics occur more frequently in the elderly (>60 years) and may be more severe. These patients should be carefully monitored for the development of diarrhea.

Pharmacokinetic studies with clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration.

ADVERSE REACTIONS

The following reactions have been reported with the use of clindamycin.

Gastrointestinal: Antibiotic-associated colitis (see WARNINGS), pseudomembranous colitis abdominal pain, nausea and vomiting. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see WARNINGS). An unpleasant or metallic taste occasionally has been reported after intravenous administration of the higher doses of clindamycin phosphate.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have also been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions.

Skin and Mucous Membranes: Pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported. (See *Hypersensitivity Reactions*).

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Renal: Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

Hematopoietic: Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

Musculoskeletal: Rare instances of polyarthritis have been reported.

Cardiovascular: Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration. (See DOSAGE AND ADMINISTRATION section)

OVERDOSAGE

Significant mortality was observed in mice at an intravenous dose of 855 mg/kg and in rats at an oral or subcutaneous dose of approximately 2618 mg/kg. In the mice, convulsions and depression were observed.

Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

DOSAGE AND ADMINISTRATION

If diarrhea occurs during therapy, this antibiotic should be discontinued. (See WARNING box).

Adults: Parenteral (IM or IV Administration): Serious infections due to aerobic gram-positive cocci and the more susceptible anaerobes (NOT generally including *Bacteroides fragilis, Peptococcus* species and *Clostridium* species other than *Clostridium perfringens*):

600-1200 mg/day in 2, 3 or 4 equal doses.

More severe infections, particularly those due to proven or suspected *Bacteroides fragilis, Peptococcus* species, or *Clostridium* species other than *Clostridium perfringens*:

1200-2700 mg/day in 2, 3 or 4 equal doses.

For more serious infections, these doses may have to be increased. In life-threatening situations due to either aerobes or anaerobes these doses may be increased. Doses of as much as 4800 mg daily have been given intravenously to adults. See Dilution and Infusion Rates section below.

Single intramuscular injections of greater than 600 mg are not recommended.

Alternatively, drug may be administered in the form of a single rapid infusion of the first dose followed by continuous IV infusion as follows:

To maintain serum clindamycin levels	Rapid infusion rate	Maintenance infusion rate
Above 4 mcg/mL	10 mg/min for 30 min	0.75 mg/min
Above 5 mcg/mL	15 mg/min for 30 min	1 mg/min
Above 6 mcg/mL	20 mg/min for 30 min	1.25 mg/min

Neonates (less than 1 month): 15 to 20 mg/kg/day in 3 to 4 equal doses. The lower dosage may be adequate for small prematures.

Pediatric patients (1 month of age to 16 years): Parenteral (IM or IV) administration: 20 to 40 mg/kg/day in 3 or 4 equal doses. The higher doses would be used for more severe infections. As an alternative to dosing on a body weight basis, children may be dosed on the basis of square meters body surface: 350 mg/m^2/day for serious infections and 450 mg/m^2/day for more severe infections.

Parenteral therapy may be changed to clindamycin palmitate hydrochloride for oral solution or clindamycin hydrochloride capsules when the condition warrants and at the discretion of the physician.

In cases of ß-hemolytic streptococcal infections, treatment should be continued for at least 10 days.

Dilution and Infusion Rates: Clindamycin phosphate must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg per mL. Infusion rates should not exceed 30 mg per minute. The usual infusion dilutions and rates are as follows:

Dose	Diluent	Time
300 mg	50 mL	10 min
600 mg	50 mL	20 min
900 mg	50 - 100 mL	30 min
1200 mg	100 mL	40 min

Administration of more than 1200 mg in a single 1 hour infusion is not recommended.

Dilution and Compatibility: Physical and biological compatibility studies monitored for 24 hours at room temperature have demonstrated no inactivation or incompatibility with the use of clindamycin phosphate in IV solutions containing sodium chloride, glucose, calcium or potassium, and solutions containing vitamin B complex in concentrations usually used clinically. No incompatibility has been demonstrated with the antibiotics cephalothin, kanamycin, gentamicin, penicillin or carbenicillin.

The following drugs are physically incompatible with clindamycin phosphate: ampicillin sodium, phenytoin sodium, barbiturates, aminophylline, calcium gluconate, and magnesium sulfate.

The compatibility and duration of stability of drug admixtures will vary depending on concentration and other conditions.

Physico-Chemical Stability of Diluted Solutions of Clindamycin:
Room temperature: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 16 days at 25°C. Also, 18 mg/mL (equivalent to clindamycin base) in 5% Dextrose Injection, in minibags, demonstrated physical and chemical stability for at least 16 days at 25°C.

Refrigeration: 6, 9 and 12 mg/mL (equivalent to clindamycin base) 5% in dextrose injection, 0.9% sodium chloride injection, or Lactated Ringer's Injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 32 days at 4°C.

IMPORTANT: This chemical stability information in no way indicates that it would be acceptable practice to use this product well after the preparation time. Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

Frozen: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection in minibags demonstrated physical and chemical stability for at least eight weeks at -10°C.

Frozen solutions should be thawed at room temperature and not refrozen.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

- Established Name
- Strength
- Packaging, NDC number(s)
- Dosage form, color
- Special handling and storage recommendations

ANIMAL TOXICOLOGY

One year oral toxicity studies in Spartan Sprague - Dawley rats and beagle dogs at dose levels up 300 mg/kg/day (approximately 1.1 and 3.6 times the highest recommended adult human dose based on mg/m^2, respectively) have shown clindamycin to be well tolerated. No appreciable difference in pathological findings has been observed between groups of animals treated with clindamycin and comparable control groups. Rats receiving clindamycin hydrochloride at 600 mg/kg/day (approximately 2.1 times the highest recommended adult human dose based on mg/m^2**)** for 6 months tolerated the drug well; however, dogs dosed at this level (approximately 7.2 times the highest recommended adult human dose based on mg/m^2) vomited, would not eat, and lost weight.

REFERENCES

1. Smith RB, Phillips JP: Evaluation of Clindamycin Hydrochloride and Clindamycin Phosphate in an Aged Population. Upjohn TR:8147-9122-021, December 1982.

2. Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic susceptibility testing by a standardized single disk method, *Am J Clin Path*, **45**:493-496, 1966. Standardized Disk Susceptibility Test, *Federal Register* **37**:20527-29, 1972.

3. National Committee for Clinical Lab. Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria-Second Edition; Tentative Standard. NCCLS publication M11-T2. Villanova, PA; NCCLS; 1988.

CONTAINER/CARTON

In addition to the general label requirements("℞ only" statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name and strength should read as follows:

  Clindamycin Phosphate Injection, USP

300 mg/2 mL* (150 mg/mL)	or	300 mg/2 mL (150 mg/mL) equivalent to clindamycin

- For IM or IV Use

- Dilute Before IV Use

Side Panel:

- If space permits, include an "Each mL contains..." statement and "Usual Dosage: See Package Insert" statement.

- If manufacturing multiple strengths, we encourage you to differentiate your product strengths by boxing, contrasting colors or some other means.

- We recommend that "℞ only" appear prominently on the principal display panel.